A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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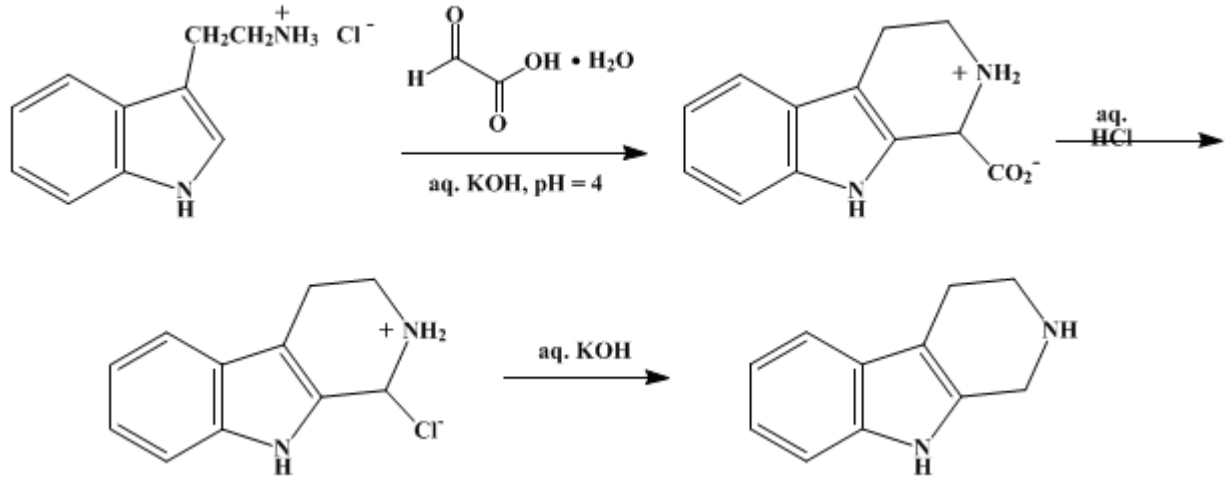
1,2,3,4-TETRAHYDRO-β-CARBOLINE

[1*H*-Pyrido[3,4-*b*]indole, 2,3,4,9-tetrahydro-]



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1. Procedure

In a 1-l. Erlenmeyer flask, 25 g. (0.13 mole) of tryptamine hydrochloride (Note 1) is dissolved in 400 ml. of water by stirring and warming on a steam bath to approximately 45°. After cooling to room temperature, a solution of 13.2 g. (0.143 mole) of glyoxylic acid monohydrate (Note 2) in 30 ml. of water is added followed by the slow addition (about 3 minutes) of a cooled solution of 7.05 g. (0.126 mole) of potassium hydroxide in 35 ml. of water (Note 3). Precipitation of tetrahydro-β-carboline-1-carboxylic acid takes place during the addition of the potassium hydroxide solution or soon thereafter. After stirring at ambient temperature for 1 hour, the solid is collected on a filter and washed thoroughly with 100 ml. of water. The damp filter cake is transferred to a 1-l. beaker and suspended in 240 ml. of water; 34 ml. of concentrated hydrochloric acid is slowly added (Note 4) with stirring. The mixture is boiled on a hot plate for 30 minutes before an additional 35 ml. of concentrated hydrochloric acid is added. Heating is continued for another 15 minutes, and the resulting solution is allowed to cool to room temperature. The precipitated hydrochloride salt is collected on a filter and washed with 30 ml. of water. The product is dissolved in 400 ml. of water by stirring and warming on a steam bath to approximately 55°, and the solution is adjusted to pH 12 with 20% aqueous potassium hydroxide (approximately 50 ml. is required). After cooling to room temperature, the product is collected by suction filtration, washed with 400 ml. of water, and dried in a vacuum desiccator over phosphorus pentoxide, yielding 17.0–17.6 g. (78–80%) of 1,2,3,4-tetrahydro-β-carboline, m.p. 204–205° (Note 5); ^{1}H NMR spectrum (dimethyl sulfoxide-d_6): δ 2.70 (t, 2H, CH_2CH$_2$N), 2.72 (s, 1H, N*H*), 3.00 (t, 2H, CH$_2$CH_2N), 3.85 (s, 2H, CCH_2N), 6.80–7.50 (m, 4H, C$_6H_4$), and 10.53 (s, 1H, N*H*).

2. Notes

1. The checkers used tryptamine hydrochloride (m.p. 253–255°) purchased from Regis Chemical Company.
2. Glyoxylic acid monohydrate is available from Pierce Chemical Company.
3. The resulting solution should have a pH between 3.5 and 4.0; if not, it should be adjusted with either potassium hydroxide or hydrochloric acid solution.
4. If all the hydrochloric acid is added at once, foaming makes the reaction unmanageable.
5. The melting point agrees with that of the literature[2] and is unchanged on recrystallization of the product from ethanol.

3. Discussion

1,2,3,4-Tetrahydro-β-carboline has been prepared by the condensation of tryptamine with formaldehyde in the presence of sulfuric acid[3] and has also been obtained as a by-product in the acid-catalyzed esterification of 1,2,3,4-tetrahydro-β-carboline-1-carboxylic acid.[2]

The described two-step procedure is uncomplicated and can be carried out in 1 day, giving in good yield a product that does not require further purification. This procedure has been used for the preparation of 3-methyl-, 9-methyl-, and 6-methoxy-1,2,3,4-tetrahydro-β-carboline[4] and has been modified for 9-phenyl-1,2,3,4-tetrahydro-β-carboline.[5] The method is generally applicable to the preparation of other 1-unsubstituted tetrahydro-β-carbolines providing the 1-carboxylic acid precursor is soluble in the hot acid used to effect decarboxylation.

Reviews of the chemistry of the carbolines have been published.[6,7]

References and Notes

1. Texas Research Institute of Mental Sciences, Texas Medical Center, Houston, Texas 77025.
2. Z. J. Vejdelek, V., Trcka, and M. Protiva, *J. Med. Pharm. Chem.*, 3, 427 (1961).
3. E. Späth and E. Lederer, *Ber. Dtsch. Chem. Ges.*, 63, 2102 (1930).
4. B. T. Ho, W. M. McIsaac, K. E. Walker, and V. Esteves, *J. Pharm. Sci.*, 57, 269 (1968).
5. B. T. Ho, W. M. McIsaac, and K. E. Walker, *J. Pharm. Sci.*, 57, 1364 (1968).
6. W. O. Kermack and J. E. McKail, in R. C. Elderfield, "Heterocyclic Compounds," Vol. 7, Wiley, New York, 1961, p. 237.
7. R. A. Abramovitch and I. D. Spenser, *Adv. Heterocycl. Chem.*, 3, 79 (1964).

Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

3-methyl-, 9-methyl-, and 6-methoxy-1,2,3,4-tetrahydro-β-carboline

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid,
hydrochloride (7647-01-0)

formaldehyde (50-00-0)

potassium hydroxide (1310-58-3)

1,2,3,4-Tetrahydro-β-carboline,
tetrahydro-β-carbolines,
1H-Pyrido[3,4-b]indole, 2,3,4,9-tetrahydro- (16502-01-5)

tryptamine hydrochloride (343-94-2)

glyoxylic acid monohydrate (6000-59-5)

1,2,3,4-tetrahydro-β-carboline-1-carboxylic acid,
tetrahydro-β-carboline-1-carboxylic acid

9-phenyl-1,2,3,4-tetrahydro-β-carboline

tryptamine (61-54-1)

phosphorus pentoxide (1314-56-3)